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Clinical report

# 3 generation pedigree with paternal transmission of the 22q11.2 deletion syndrome: Intrafamilial phenotypic variability

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ABSTRACT

In this case report, we present a paternal transmission of a classic 3 Mb 22q11.2 deletion syndrome (22q11.2 DS) in a 3 generation family. In this family a young girl, her father, her uncle and her grandfather were diagnosed with this disorder. All carriers showed phenotypic expression, there were no unaffected siblings in the second or third generation. Presenting symptoms in the patient in first generation (grandfather) were psoriatic arthritis, thrombocytopenia and a right aortic arch. There was no intellectual disability. The second generation uncle was known with a severe intellectual disability, mild facial characteristics, a septal defect and a clubfoot, whereas the second generation father had a tetralogy of Fallot, no intellectual disability and minimal facial characteristics. The third generation daughter had a moderate intellectual disability, hypernasal speech, triphalangeal thumb, severe speech and language development delay, pronounced facial characteristics and a diagnosis of ADHD. It was notable that the expression in the two brothers of the second generation gives two very different clinical phenotypes with a severe intellectual disability in the oldest brother. This report describes a pronounced clinical variability in a 3 generation familial 22q11.2 deletion with paternal transmission. We can assume that several mechanisms play an important role in the heterogeneity and part of the answer should be found in the genetic background underlying the 22q11.2 deletion. In addition in this family the neuropsychiatric phenotype and intellectual disability seem to be associated with a lower level of social and occupational functioning while a congenital heart disease does not. This clinical report illustrates that a detailed description of these patients can be very informative and still increase the knowledge on this heterogonous syndrome. For the clinicians working with these patients it emphasizes the need for a multidisciplinary approach that takes into account the individual needs.



## 1. Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is a phenotypically heterogenous syndrome caused by a hemizygous microdeletion at the q11.2 region of chromosome 22. Next to being the most common microdeletion syndrome with an estimated overall prevalence of 1 in 4000 live births [Oskarsdóttir et al., 2004], it is also characterized by a higher phenotypic variability compared to other micodeletion syndromes f.e. Williams or Prader–Willi syndrome. The phenotypic expression of this deletion is complex and varies ranging from facial dysmorphism, congenital heart defects, hypocalcemia, palate defects, immunodeficiency, neurodevelopmental delays and learning difficulties to psychiatric disorders [McDonald-McGinn and Sullivan, 2011]. More than 180 clinical features, both physical and behavioral, have been described. Several mechanisms have been proposed to be responsible for this phenotypic variability. Decreased gene dosage of multiple genes is believed to be involved in phenotypic expression [Meechan et al., 2011]. The size of the 22q11.2 deletion is in approximately 87% of patients a deletion of about 3 Mb containing about 60 genes, and around 8% carry a smaller deletion of about 1.5 Mb containing about 35 genes [ Shaikh et al., 2000]. Until now, there is no correlation found between the

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size of the deletion and phenotypic expression [Michaelovsky et al., 2012], though it is accepted that deletion of the 1.5 Mb region can induce a full-scale clinical picture and therefore the 1.5 Mb region is called the critical deletion region. Identification of the microdeletion can be performed through different molecular techniques. Until several years ago, fluorescence in situ hybridization (FISH) and MLPA were commonly used to ascertain a diagnosis after clinical suspicion of a 22q11 DS. More recently, chromosomal microarray technologies (array CGH) are implemented to identify the 22q11.2 deletion in a proband, having the advantage of being able to screen the entire genome for submicroscopic rearrangements. In more than 90% of cases, the deletion occurs de novo, in the remaining 10% the deletion is inherited from the affected parent (*familial deletion*) [McDonald-McGinn et al., 2001]. The inheritance pattern is autosomal dominant. In this case report, we present for the first time a 3 generation family with a paternal transmission of a 22q11.2 DS.

## 2. Case presentation

We present a three generation pedigree, with four individuals carrying a 22q11.2 DS. In all affected individuals, paternal transmission of the deletion was observed. The index patient, II.1 (see Fig. 1), is an adult man living in a residential setting for people with moderate to severe intellectual disability (ID) In search for a possible explanation for his behavioral problems, ID and facial dysmorphism, a clinical genetic evaluation was requested. Array CGH revealed the typical ~3 Mb microdeletion at the 22q11.2 region (Fig. 2).

Around the same time, the daughter of the youngest brother (III.1) was evaluated at our department, at age 4 years. She was referred because of distinct facial characteristics and presence of a pronounced developmental delay in several domains such as fine and gross motor skills, speech, language and cognition. FISH confirmed the clinical suspicion of a 22q11.2 DS.

Subsequent family screening using FISH revealed that both father (II.3) and grandfather (I.1) carried the microdeletion at 22q11.2. There was a miscarriage of the second child (II.2, also a boy) at 6 months of pregnancy, of unknown cause and there was no further genetic information available.

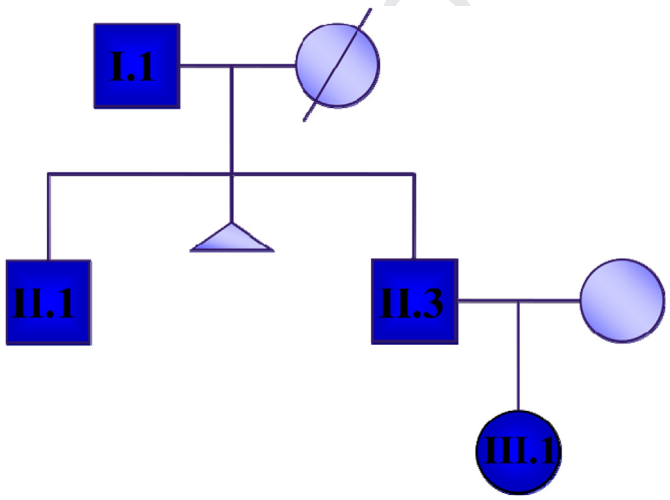


**Fig. 1.** Pedigree of the 3-generation family in this report. Blue colored boxes are the individuals with a 22q11.2DS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### 2.1. Medical history and clinical features

On clinical investigation I.1 would not have been suspected of having a 22q11.2 deletion, except for some very mild facial characteristics. Compared to the other family members with 22q11.2DS, he has a limited medical history encompassing regular follow-ups for his psoriatic arthritis, a right aortic arch and a diagnosis of mild thrombocytopenia (136,000/microL in 2006; 139,000/microL in 2013). His youngest son II.3 has an extensive cardiac history with corrective cardiac surgery at an early age for a Tetralogy of Fallot and several cardiac surgical procedures later in life. This included a Bentall procedure because of an ascending aortic aneurysm with a dilated aortic root and aortic insufficiency, and a pacemaker to treat a third-degree atrioventricular block. The oldest brother II.1 also had a septal defect, mild scoliosis and mild thrombocytopenia. The granddaughter III.1 had a triphalangeal thumb, pointed fingers and pronounced facial features including plagiocephaly, a pronounced nasal bridge, deep-set eyes, small ears and a small mouth with a short philtrum. She was hospitalized at several occasions because of recurrent bronchopneumonia. A severe speech delay with very hypernasal speech was present although video faryngography excluded velopharyngeal insufficiency. Cardiac examination, including echocardiography was normal.

### 2.2. Development, cognition and psychiatric history

I.1 does not have any psychiatric history or psychological problems in the past or present. His psychomotor development was normal and his IQ could be estimated at a low average level. His youngest son II.3 has about the same intellectual and psychological profile with a low average IQ and no psychiatric history (Table 1).

In contrast, patient II.1 had been institutionalized in a residential setting for people with moderate to severe intellectual disabilities after several hospitalizations in psychiatric wards because of behavioral problems such as running away and aggressive attacks. During early childhood, a moderate to severe delay of motor skills, speech and cognition was noticed. In 2004 at age 33, psychomotor testing showed a basic motor age of 2 years and an effective motor age of 3 years 8 months. McCarthy development scales revealed a verbal level of 5 years 3 months, a performance level of 5 years, a quantitative level of 6 years 9 months, general cognition at 5 years 3 months and memory at 5 years 6 months. Language assessment with the Reynell developmental language test (RDLT) revealed a language level of 3 years 9 months on the comprehension scale, 4 years on the expressive scale and 3 years and 9 months on the total language scale. At the time of diagnosis of 22q11 DS at age 39, he had been living in the residential care for people with a severe ID for about 6 years. He had been diagnosed with autism spectrum disorder (ASD) in the past. At age 28 his full scale IQ (FSIQ) was estimated at 35. At age 43 neurocognitive testing revealed a verbal level of 5 years 3 months, a performance level of 4 years 4 months and a total level of 4 years 7 months. Caregivers needed an adapted way to communicate with him and handle his behavioral problems. It took several years before the aggressive attacks and running away diminished. Although the use of physical restraints was at times still necessary, caregivers noted that he was more at ease.

III.1 presented with a moderate developmental delay both on motor and on verbal development with start of walking at 23 months, slow and indistinct speech, and difficulties with toilet training. At the age of 3, 5 years, Peabody developmental motor scales (PDMS) showed a gross motor quotient of 70 and a fine motor quotient of 58, both scoring below the 1st percentile for her age. Reynell Developmental Language Scales revealed scores below the 1st percentile for her age on the two subscales and the total


**Fig. 2.** Pictures of the 4 individuals with a 22q11.2DS. Arrows are used to identify each individual.

**Table 1**
Overview of the characteristics in the affected individuals.

| | I.1 | II.1 | II.2 | III.1 |
|---|---|---|---|---|
| AGE | 66y | 43y | 35y | 7y |
| Age at diagnosis | 63y | 39y | 31y | 3y |
| Diagnostic Tool | FISH | CGH-array | FISH | FISH |
| **Medical history:** | | | | |
| Cardiopathy | RAA | Septal defect | TOF + RAA | None |
| Inflammatory diseases | Psoriatic arthritis | None | None | Recurrent bronchopneumonia |
| Hematology | Thrombocytopenia (mild) | Thrombocytopenia (mild) | None | None |
| Speech and palate function | Normal | Studder | Normal | Verbal developmental dyspraxia |
| Body features | Very mild facial features | Mild scoliosis<br>Overcorrected clubfeet | Mild facial features | Plagiocephaly<br>Pronounced Nosebridge<br>Deep-set eyes<br>Small ears<br>Small mouth<br>Short philtrum<br>Pointed fingers |
| **Development, cognition and psychiatric history:** | | | | |
| Motor skills | – | Start walking at 19 months<br>BMA = 2y<br>EMA = 3y 8m | – | Start walking at 23 months<br>GMQ < 1st pctl<br>FMQ < 1st pctl |
| Language and speech | – | At age 33y<br>CLS = 3y 9m<br>ELS = 4y<br>TLS = 3y 9m | – | Slow speech development<br>CLS < 1st pctl<br>ELS < 1st pctl<br>TLS < 1st pctl |
| Psychiatric diagnoses | None | - Behavioral problems with oppositional behavior<br>- Impulse control disorder, unspecified<br>- ASD diagnosis | None | ADHD |
| IQ | Low average | Severe ID<br>FSIQ ± 35 at age 28 | Low average | Mild-moderate ID<br>FSIQ ± 59 at age 5 |
| **Social and occupational functioning:** | | | | |
| Social | + | Very limited | + | + |
| Work | Retirement | Residential care | Full time job | / |

Abbreviations: RAA = right aortic arch; TOF = Tetralogy of Fallot; BMA = basic motor age; EMA = effective motor age; GMQ = gross motor quotient; FMQ = fine motor quotient; CLS = comprehensive language score on the Reynell Developmental Language Scales (RDLS); ELS = Expressive Scale score on RDLS; TLS = total scale score on RDLS; ASD = autism spectrum disorder; ADHD = attention deficit and hyperactivity disorder; ID = intellectual disability; FSIQ = Full Scale Intelligence Quotient.



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scale corresponding to an age below 2.0 years old. . Using the GOS (Groningse Ontwikkelingsschaal), a Dutch adaptation of the Kaufman Assessment Battery for Children, FSIQ was estimated at 59 at age 5 years. After trying the first year of preschool, she changed to a school with a special needs education program and an intensive revalidation/rehabilitation program was started for the specific developmental delays and deficits.

### 2.3. Adaptive and social functioning

Comparing the levels of social and occupational functioning between the four family members, we noticed that the grandfather I.1 had a good social and occupational functioning. He was able to work until his retirement, was married, raised his two sons and was able to handle the challenges with his oldest son (II.1).

Patient II.3, despite his severe cardiac disorder, had a good level of social and occupational functioning. He was able to finish vocational school, find a job and start a family. He works as a truck driver and spends most of his time on the road driving through foreign countries, depends on himself to solve encountered problems.

In contrast, his older brother II.1 carrying the same deletion, grew up in the same family but has been living institutionalized for more than two decades; first in a psychiatric setting and afterwards in a residence with specialized care for individuals with a severe intellectual disabilities. He needs help 24 h a day, 7 days a week and is always accompanied by a caregiver when going out. Because social interactions were very stressful and evoked behavioral problems, visits were limited to his nearest family once a week. Organized events were not shared with him beforehand because the anticipation made him high strung and caused physical complaints and behavioral problems. II.1 lives in a day to day world that is organized by his caregivers.

The youngest family member III.1 has been able to gain a moderate level of functioning with the support of a specialized educational program, an adapted school environment and medication for ADHD.

## 3. Discussion

This report describes a pronounced clinical variability in a 3 generation familial 22q11.2 deletion with paternal transmission. Although it has been described that the prevalence of males with a paternal transmission of the 22q11.2 deletion is much lower than maternal transmission [Thomas et al., 2006; Torres-Juan et al., 2007], the phenotypic expression and the clinical variability seem to be comparable to the known high phenotypic variability in the total 22q11.2DS population [Cirillo et al., 2014; Digilio et al., 2003].

An aggravation of the phenotype over the three generations is observed for developmental delay, speech delay, IQ and facial features but not for immune dysfunction or congenital heart defects, contrasting with the findings of Cirillo et al. [2014]. If looking only at the first and second generation we observe an aggravation of the cardiac phenotype with I.1 only having a right aortic arch while both of his sons II.1 and II.3 were diagnosed with a cardiac malformation, respectively a septal defect and a Tetralogy of Fallot. On the other hand, going from second to third generation this pattern does not continue with III.3 having no cardiac features of 22q11.2 DS. We can speculate that the aggravation noted in earlier studies could be in part biased by the diagnostic process in which the second generation most of the time is the person first to be diagnosed because of the clinical presentation, and the first generation parents are most of the time diagnosed through screening afterwards. In most cases, the cardiac phenotype seems to be the reason for referral to genetic counseling, especially in infancy before the age of 2 years [Cancrini et al., 2014; Oskarsdottir et al., 2005]. Another contributing factor could be that a more severe phenotype seems to cause a stronger negative selective pressure, both because of biological and sociological disadvantages. In the older generations of 22q11.2 DS patients, the presence of a severe CHD caused a negative selection. In the past, severe CHD or immunodeficiency had higher mortality rates. Renewed cardiac surgical procedures and stem cell transplantation have lowered the mortality rates and it no longer seems to be an important factor in reduced reproductive fitness. However it has been shown recently that certain neuropsychiatric phenotypes and intellectual disabilities were significant negative predictors of reproductive fitness [Costain et al., 2011]. Also a different impact was found between the two sexes with a lower reproductive fitness in men compared to women [Costain et al., 2011].

Several mechanisms could be responsible for the pronounced clinical variability in this three generation family and the presence of an increasing complexity and severity of the symptoms in subsequent/consecutive generations within this limited pool of genetic information. With regard to the intellectual disability in the third generation (III.1), an aggravation seems to be present compared to second (II.3) and first generation (I.1). Current findings indicate that the genetic architecture of intellectual disability is complex and a wide variability in intelligence has been found in the 22q11.2DS population ranging from normal intelligence to moderate-severe intellectual disability. They have found a lower IQ in familial compared to de novo deletions [De Smedt et al., 2007]. Proposed explanations were a lower educational attainment level of the parents of children with familial inherited deletions, and assortative mating, resulting in a lower educational level in the unaffected parent. Studies also have found a role for the genetic variation within the 22q11.2 region [Gothelf et al., 2005], for environmental factors such as socioeconomic status [Shashi et al., 2010] but also parental IQ and siblings IQ [Olszewski et al., 2014]. Additionally several factors contributing to the variability in IQ (possibly playing a role in the variability and aggravation within this family) have not yet been systematically studied. To explain this variability future studies should look at the role of assortative mating and the genetic background, but also investigate the role of other environmental factors such as social support, therapy and coping strategies [Swillen & McDonald-McGinn, submitted]. Q5

Looking at the phenotypic variability within this family the difference between the 2 s generation brothers (II.1 and II.3) is notable. The intellectual disability and behavioral problems of II.1 seem to be more severe than expected in a 22q11.2 DS and are in contrast with the lack of neuropsychiatric problems and intellectual disability in the younger brother (II.3). A more severe or complex clinical presentation (such as a severe intellectual disability or severe developmental delay) could be explained by a so called second hit. In broad terms, a second hit could be defined as a genetic, epigenetic or environmental insult that has an important influence on the phenotypic expression. Studies have shown that a more severe or complex clinical presentation is associated with a higher prevalence of additional large copy number variations (CNV's) [Kumar, 2010; Girirajan et al., 2012]. The presence of two large CNV's of unknown clinical significance was associated with an eight times increased presence of a developmental delay [Girirajan et al., 2012]. Within a population of pediatric cases with a 16p12.1 microdeletion the presence of a second large CNV was associated with an additional or more severe phenotypes compared to the classical phenotype [Girirajan et al., 2010]. However, in subject II.2 no other relevant CNV could be detected by the 105k array CGH. This observation is in line with the study from Bassett et al. [2008] that found no evidence for a general increase of de novo CNVs in 22q11.2DS in a cohort of 100 adults with 22q11.2DS compared with controls [Bassett et al., 2008].



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Most of the clinical features described in this report have already been linked to the 22q11.2DS in the literature. Two exceptions are the psoriatic arthritis in I.1 and the triphalangeal thumb of III.1 for which we couldn't find a direct association with the presence of a 22q11.2 deletion in the literature. In our center we have at least one other patient with a 22q11.2DS, that had a triphalangeal thumb. It could be that this is a less frequent but important clinical feature of the 22q11.2 DS. The psoriatic arthritis falls in line with the literature that describes the presence of an auto-immune disease, including the full range of possibilities, in 8–10% of the 22q11.2 DS patients [Lima et al., 2011].

In this family the neuropsychiatric phenotype and intellectual disability are associated with a lower level of social and occupational functioning while a congenital heart disease does not. In adults with 22q11.2 DS a correlation was found between IQ and adaptive functioning skills, with IQ as a significant predictor of functional impairment. Congenital heart disease and history of mood/anxiety disorders were not significant predictors of functioning [Butcher et al., 2012]. In children and adolescents, the relationship between IQ and adaptive functioning remains unclear with different studies giving conflicting results [Angkustsiri et al., 2012; Dewulf et al., 2013].

In conclusion, a pronounced variability in phenotypic expression was found in this three generation 22q11.2deletion family. There are arguments that suggest that the phenotype gets more severe and complex in second and third generation, with an aggravation of the neuropsychiatric phenotype giving a lower IQ, psychiatric symptoms and behavioral problems. Cardiac or other somatic phenotypes do not seem to aggravate but there is a pronounced intrafamilial variability. We can assume that several mechanisms play an important role in this heterogeneity and part of the answer should be found in the genetic background underlying the 22q11.2 deletion. Hopefully further research comparing this genetic background in large groups of 22q11.2DS patients focusing on the presence or absence of specific clinical characteristics could identify the genetic causes of this variation. It is important to not only focus on the clinical variability of this syndrome but also on the impact of level intellectual and adaptive functioning. As a consequence of this variability, all individual family members are differently affected in social, occupational and adaptive functioning and therefore need a personalized care. This report emphasizes the need for a multidisciplinary approach for this population taking into account the individual needs. It stresses the importance of a good standardized baseline examination, but also regular follow-ups to adapt the care to the changing needs of the patients.

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